REMARKS

Claim Rejections under 35 U.S.C. § 103(a):

(1) Claims 11-15 and 17-19 over Badylak (2002) in view of Badylak (2007)

The Examiner has rejected claims 11-15 and 17-19 under 35 U.S.C. § 103 as being obvious over WO 98/25637 or U.S. Patent No. 6,379,710 ("Badylak (2002)") each in view of U.S. Patent No. 7,175,841 ("Badylak (2007)"). Independent claims 11 and 19 of the instant application describe a basement membrane graft construct wherein the DNA content "is within a set of values with an average of 0.303 and a standard deviation of 0.263 micrograms of DNA per milligram of dry weight of the basement membrane."

The arguments that refer to "Badylak (2002)" in this response apply to either WO 98/25637 or Badylak (2002) because Badylak (2002) is a U.S. patent corresponding to WO 98/25637. The Examiner contends that Badylak (2002) teaches a tissue graft composition comprising liver basement membrane prepared by removing the cellular components from liver tissue. However, the Examiner concedes that Badylak (2002) does not teach a specified DNA content of the liver basement membrane.

The Examiner contends that Badylak (2007) teaches an improved tissue graft construct comprising submucosa of a warm-blooded vertebrate and a preselected group of eukaryotic cells to enhance the repair of damaged or diseased tissue *in vivo*. In addition, the Examiner asserts that Badylak (2007) describes the DNA content of cartilaginous tissue, formed on an intestinal submucosa composition to be about 0.86 +/- 0.2 μg DNA/mg dry weight. Moreover, the Examiner argues that Badylak (2007) describes that intestinal submucosa has a DNA content of 2.04 +/- 0.1 μg DNA/mg dry weight. Therefore, according to the Examiner, it would have been *prima facie* obvious for a person skilled in the art to

employ the tissue graft composition comprising liver basement membrane of Badylak (2002) with the DNA content in the tissue graft taught by Badylak (2007) to arrive at the invention described by Applicants' claims, where grafts comprising basement membrane have a DNA content within a set of values with an average of 0.303 and a standard deviation of 0.263 micrograms of DNA per milligram of dry weight of the basement membrane. Specifically in regards to Badylak (2007), the Examiner states that "[i]t would be obvious to one of ordinary skill in the art to prepare the liver basement membrane composition having the claimed DNA content since ... determining the DNA content of a tissue graft and to have [sic] various different DNA contents in various tissue graft [sic] would be obvious to one of ordinary skill." Applicants respectfully traverse the Examiner's rejection. Claims 11-15 and 17-19 of the instant application are not obvious over Badylak (2002) in view of Badylak (2007).

DNA CONTENT OF CARTILAGINOUS TISSUE CELLS IS IRRELEVANT

First, the DNA content of cartilaginous tissue formed on an intestinal submucosa composition as described in Badylak (2007) is irrelevant compared to the invention as defined by Applicants' claims. Badylak (2007) describes the DNA content of cartilaginous tissue formed on an intestinal submucosa composition to be about 0.86 +/- 0.2 μg DNA/mg dry weight (see column 21, lines 11-29). Importantly, this described DNA content is an estimated quantification of cartilaginous tissue (i.e., chondrocyte ***cells***) grown *in vitro* on intestinal submucosa. The methods employed in Badylak (2007) to calculate the DNA content of cartilaginous tissue state that the content "was estimated by correcting for the intestinal submucosa contribution" (see column 19, lines 4-7). In other words, the estimated DNA content of cartilaginous tissue as cited by the Examiner is only for cartilaginous cells grown *in vitro*, ***not*** an assessment of the DNA content for the intestinal submucosa component of the graft.

In contrast, Applicants' claims are directed to the DNA content of the basement membrane ***component*** of the graft composition. Therefore, the range of DNA content cited by the Examiner for cartilaginous tissue cells (i.e., 0.86 +/- 0.2 μg DNA/mg dry weight) is irrelevant compared to the DNA content of basement membrane as required by Applicants' claims. Accordingly, the Examiner's reliance on the DNA content of 0.86 +/- 0.2 μg DNA/mg dry weight cannot be relied upon to support a rejection of obviousness under 35 U.S.C. § 103.

OBVIOUSNESS OF RANGES

Applicants point the Examiner to MPEP § 2144.05, regarding the obviousness of ranges in claims. According to the MPEP, if "the claimed ranges overlap or lie inside ranges disclosed by the prior art[,] a *prima facie* case of obviousness exists." MPEP § 2144.05(I) (quoting *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976)). Furthermore, "a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties." *Id.* (quoting *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)).

A careful analysis of Applicants' independent claims 11 and 19 reveals that the ranges in Applicants' claims do ***not*** overlap or lie inside ranges disclosed by the prior art (i.e., Badylak (2007)). Applicants' claims describe a range of the DNA content in basement membrane wherein the DNA content is within a set of values with an average of 0.303 and a standard deviation of 0.263 micrograms of DNA per milligram of dry weight of the basement membrane. Taking into account the stated standard deviation, the claims thus describe the DNA content of basement membrane with a range of 0.040 μg DNA/mg dry weight to 0.566 μg DNA/mg dry weight.

In contrast, the range of the DNA content of intestinal submucosa tissue as disclosed by Badylak (2007) does *not* overlap Applicants' claimed range of the DNA content.

Badylak (2007) describes that the DNA content of intestinal submucosa tissue is 2.04 +/- 0.1 μg DNA/mg dry weight. Taking into account the stated standard error, Badylak (2007) thus describes the DNA content of intestinal submucosa tissue with a range of 1.94 μg DNA/mg dry weight to 2.14 μg DNA/mg dry weight.

For the Examiner's convenience, the ranges of the DNA content as described in Applicants' claims and in the prior art (i.e., Badylak (2007)) are summarized in Table 1:

Table 1.

Claims of Instant Application or Prior Art Reference	Tissue Type	DNA Content (μg DNA/mg dry weight)	Range of DNA Content (μg DNA/mg dry weight)
Independent claims 11 and 19 (instant application)	Basement membrane	0.303 +/- 0.263	0.040 - 0.566
Badylak (2007) (prior art reference)	Intestinal submucosa tissue	2.04 +/- 0.1	1.94 - 2.14

Clearly, the range of the DNA content of basement membrane as described in independent claims 11 and 19 of the instant application does *not* overlap the range of the DNA content of intestinal submucosa tissue as described in the prior art (see Table 1, above).

Moreover, the DNA content range stated in Applicants' claims and the DNA content range described in Badylak (2007) are not close enough that one skilled in the art would have expected them to have the same properties. It is known in the art that a lower DNA content in graft compositions correlates with reduction in immunogenicity (see, for example, an abstract by Narita et al., submitted herewith as "Exhibit A"). Accordingly, one skilled in the art would not have expected a basement membrane with a DNA content range as stated in Applicants' claims (i.e., 0.303 +/- 0.263 μg DNA/mg dry weight) to have the same properties as an intestinal submucosa tissue graft with a DNA content range as stated in Badylak (2007) (i.e., 2.04 +/- 0.1 μg DNA/mg dry weight). Therefore, the Examiner has not

established a *prima facie* case of obviousness regarding obviousness of the claimed ranges as required by MPEP § 2144.

ALL CLAIM LIMITATIONS MUST BE TAUGHT OR SUGGESTED BY THE PRIOR ART

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Therefore, in order for Applicants' invention to be rendered obvious under 35 U.S.C. § 103, the combination of references relied upon by the Examiner must teach each and every element of Applicants' invention, as defined by claims 11-15 and 17-19.

The methods taught by Badylak (2002) and Badylak (2007) result in graft constructs with a DNA content higher than what is claimed in Applicants' independent claims 11 and 19. It is not obvious from the teachings of the prior art that a skilled artisan could achieve the DNA purity level claimed by Applicants. Applicants developed a new purification method to achieve the claimed DNA purity level. Furthermore, as explained above, the range of the DNA content specified by Applicants in independent claims 11 and 19 does *not* overlap with the ranges of the DNA content as described in the prior art. Accordingly, the claim limitations in claims 11 and 19 (i.e., basement membrane wherein the DNA content is 0.303 +/- 0.263 μg DNA/mg dry weight) are not taught by the prior art cited by the Examiner. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness and the rejection of claims 11-15 and 17-19 under 35 U.S.C. § 103 is improper. Withdrawal of the rejection of claims 11-15 and 17-19 under 35 U.S.C. § 103(a) over Badylak (2002) in view of Badylak (2007) is respectfully requested.

(2) Claim 19 over either Robinson et al. or Brendel et al. in view of Badylak (2007)

DNA CONTENT OF CARTILAGINOUS TISSUE CELLS IS IRRELEVANT

As discussed previously (*see* detailed arguments above), the DNA content of cartilaginous cells as described in Badylak (2007) is irrelevant compared to the invention as defined by Applicants' claims. Accordingly, the Examiner's reliance on the DNA content of cartilaginous cells cannot support a rejection of obviousness under 35 U.S.C. § 103.

OBVIOUSNESS OF RANGES

As discussed above, the range of the DNA content of basement membrane as described in independent claims 11 and 19 of the instant application does *not* overlap with the range of the DNA content of the intestinal submucosa composition as described in Badylak (2007). Furthermore, the DNA content range stated in Applicants' claims and the DNA content range described in Badylak (2007) are not close enough that one skilled in the art would have expected them to have the same properties. Therefore, the Examiner has not established a *prima facie* case of obviousness based on Robinson et al. or Brendel et al. in view of Badylak (2007).

ALL CLAIM LIMITATIONS MUST BE TAUGHT OR SUGGESTED BY THE PRIOR ART

As explained previously, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Therefore, in order for Applicants' invention to be rendered obvious under 35 U.S.C. § 103, the combination of references relied upon by the Examiner must teach each and every element of Applicants' invention, as defined by claim 19.

The proposed prior art combination of either Robinson et al. (*European Journal of Biochemistry/FEBS*, 1980, 11(2): 485-490) or Brendel et al. (*Advances in Experimental Medicine and Biology*, 1980, 131: 89-103) in view of Badylak (2007) fails to uphold a rejection based on 35 U.S.C. § 103 because all of the claim limitations in Applicants' claim 19 are not taught by the proposed reference combination. Specifically, the prior art does not teach the DNA content required by Applicants' claim 19 (*see* detailed arguments above for the

rejection under 35 U.S.C. § 103 over Badylak (2002) in view of Badylak (2007)). Claim 19 specifies that the DNA content of the basement membrane is within a set of values with an average of 0.303 and a standard deviation of 0.263 micrograms of DNA per milligram of dry weight of the basement membrane. None of the cited prior art references suggest a DNA content that is within a set of values with an average of 0.303 and a standard deviation of 0.263 micrograms of DNA per milligram of dry weight of the basement membrane. This DNA content was not predictable or identified in the prior art, and there is no suggestion in the prior art that would lead a skilled artisan to choose the specific DNA content as claimed. Applicants developed a new purification method to achieve the claimed DNA purity level.

Therefore, based on all of the foregoing arguments, claim 19 of the instant application is not obvious over the cited prior art combination. Withdrawal of the rejection of claim 19 under 35 U.S.C. § 103(a) over either Robinson et al. or Brendel et al. in view of Badylak (2007) is respectfully requested.

CONCLUSION

The foregoing amendments and remarks are believed to fully respond to the Examiner's rejections. The claims are in condition for allowance. Applicants respectfully request allowance of the claims, and passage of the application to issuance.

Respectfully submitted,

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